in vivo *28*: 1155-1158 (2014)

Primary Squamous Cell Carcinoma of the Breast After Cured Bilateral Breast Cancer

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Abstract. *Background: Primary squamous cell carcinoma (SCC) of the breast is a rare and aggressive neoplasm that constitutes approximately 0.1% of all breast carcinomas. Before the tumor can be classified as a true SCC of the breast, certain criteria need to be fulfilled. These are: i) more than 90% of the malignant cells must be of squamous cells origin; ii) tumor is independent from the overlying skin and nipple; iii) other sites of primary SCC have been excluded. Case Report: We describe a case of pure SCC of the breast that arose 15 years after local radiation for a primary adenocarcinoma of the breast in a 54-year-old woman with history of bilateral breast cancer. The tumor was triple-negative with a high Ki-67 index. The patient underwent adjuvant chemotherapy with docetaxel and oral fluorouracil. Conclusion: There are no specific guidelines for the treatment of primary SCC of the breast. Larger series are necessary to determine if different strategies of treatment and follow-up are necessary and if prognosis is really comparable to other histotypes of cancers of the breast.*

Primary squamous cell carcinoma (SCC) of the breast is a rare and aggressive form of neoplasm that constitutes approximately 0.1% of all breast cancers and confers a significantly poor survival rate (1). Before the tumor can be classified as a true SCC of the breast, certain criteria need to be fulfilled. These are: i) more than 90% of the malignant cells must be of squamous cells origin; ii) tumor is independent from the overlying skin and nipple; iii) other sites of primary SCC have been excluded (2, 3).

SCC is categorized by the World Health Organization classification of breast tumor as a purely epithelial subtype of metaplastic carcinoma as "a group of heterogeneous neoplasm characterized by a differentiation of the neoplastic epithelium into squamous cell and/or mesenchimal-looking elements" (including pure epithelial metaplastic carcinomas, squamous cell carcinoma, adenocarcinoma with spindle cell metaplasia, adenosquamous carcinoma, mucoepidermoid carcinoma and mixed epithelial/mesenchymal metaplastic carcinomas) (4).

The histopathogenesis of this neoplasms is controversial. Many studies suggest the hypothesis that SCC arises from squamous metaplasia of the breast and metaplastic differentiation is related to progesterone and estrogen levels. Stevenson *et al*., for instance, support the idea that it is an extensive and prevalent squamous metaplasia within adenocarcinoma, considering it to arise through metaplastic change of ductal carcinoma (5). Some authors, instead, suggest that it could occur as a complication of benign squamous metaplasia in breast without evidence of intraductal carcinoma. Others believe that SCC arises directly from the epithelium of the mammary ducts (6).

We present a case of pure SCC of the breast that arose 15 years after local radiation for a primary adenocarcinoma of breast.

Case Report

We describe the case of a 54-years-old Caucasian woman with no family history of breast cancer. In 1997, she was subjected to breast-conservation surgery and lymph node dissection for moderately differentiated infiltrating ductal carcinoma of the left breast of 1.1 cm in diameter. Immunohistochemistry showed positive staining for progesterone hormonal receptor and negative status for estrogen hormonal receptor. The patient received adjuvant radiotherapy and hormonal therapy with tamoxifen (20 mg) for five years. Subsequently, systematic follow-up was performed with annual clinical examination and mammography. In 2009, she was subjected to right mastectomy and lymph node dissection for a bi-focal infiltrating ductal carcinoma of the breast. The tumor was 1.6 cm in maximum

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Key Words: Primary squamous cell carcinoma of the breast, SCC, bilateral breast carcinoma, radiotherapy.

diameter, positive for hormonal receptors and epidermal growth factor receptor 2 (HER2). Two lymph nodes where metastatic out of 24 examined. The patient was treated with adjuvant chemotherapy: four cycles of fluorouracil/epirubicine/cyclophosphamide every three weeks, followed by 6 mg/m^2 trastuzumab for one year.

In March 2012 follow-up mammography was negative and the patient received adjuvant hormonal therapy with 1 mg/day anastrozol until July 2012, when she discovered a swelling in her left breast and attended our breast Unit. She underwent ultrasound of the breast that showed a mass of 8 mm with clear margins in the lower inner quadrant of the left breast. A fine-needle aspiration of the swelling was taken in August 2012. The pathologist described atypical epithelial cells and the conclusion was poorly-differentiated breast carcinoma. On September 18th, 2012 the patient was subjected to mastectomy of the left breast. Macroscopically, a grey nodule with well-circumscribed edges was found in the medial quadrants, measuring 0.6 cm in diameter. This tumor had no connection with the skin surface or the nipple.

Histologically, the neoplasm was characterized by a solid proliferation of poorly-differentiated neoplastic squamous cells, surrounded by scarce inflammatory infiltrate (Figure 1). Neoplastic cells infiltrated predominantly the adjacent stroma in the form of nests, inducing stromal reaction. These characteristics are not specific for SCC of the breast, which usually presents as a cystic lesion, where the cavity is lined by squamous cell with varying degrees of nuclear atypia and polymorphism. Inflammatory infiltrates and stromal reaction are usually prominent (4). It is important to point-out that in our case the tumor was not connected with the skin and did exhibit any glandular differentiation; furthermore, there was no evidence of lymphatic or vascular invasion. Immunohistochemistry demonstrated that there was no expression of estrogen and progesterone receptors and no overexpression of HER2 oncogene product (score 1+). The Ki-67 proliferation index was found to be high (70%). We considered this neoplasm to be a triple-negative one, in line with the known behaviour of this type of tumor. P63 is non-specific for a primary form of SCC of the breast. This protein, when positive expression is found, is useful for recognizing a squamous differentiation and for making a differential diagnosis from other types of carcinoma. We cannot not exclude the possibility of other primary sites of a squamous cell neoplasm in the patient.

Respecting the above-mentioned diagnostic criteria, the morphological findings and the immunohistochemical investigations compatible with SCC, a diagnosis of pure primary SCC of the breast was given. At this point, the patient was transferred to our Oncology Unit. Physical examination did not reveal any suspicious cutaneous palpable nodules. No signs of metastatic disease were observed on thoraco-abdominal computer tomography. Whole-body positron emission tomography did not reveal localizations. To rule-out any other primary cancer, the patient underwent gastroscopy and colonoscopy with negative results. She was also seen by gynecological, otorhinolaryngological and dermatological specialists who gave consistently negative results for the presence of other tumors. Given the exclusion of a metastatic lesion and given the histological type, degree of differentiation, hormone receptor and c-HER2 negativity and high Ki-67 index (70%) we decided to start adjuvant chemotherapy. Considering the anthracycline-based treatment for previous breast cancer and after a review of the literature. we chose a chemotherapy with three-weekly docetaxel (75 mg/m^2 day 1) and oral fluorouracil (1000 mg/m^2 twice daily for 14 days). Both drugs are indicated for the treatment of breast cancer as well as squamous carcinoma of other areas, such as the head and neck, and oesophagus. Our patient was subjected to six cycles of treatment that where well-tolerated except for grade 1 diarrhea and grade 2 neutropenia. At 18 months of follow-up, the patient is free of local and distant disease.

Discussion

Primary SCC of the breast is a very rare neoplasm, first described in 1917 and reported in about 100 cases since than (7). The rarity of cases makes it difficult to define appropriate treatment or draw conclusions about the prognosis.

Generally, SCC of the breast is more frequent during the peri- and post-menopausal age, but literature reports cases also occurring during pregnancy (8). The median age at the diagnosis is 53 years (9). Clinically, the nodule of SCC can reach considerable size and can also be mistaken for an abscess of the breast (10). Literature reports that breast abscess or other inflammatory condition may act as initial presentation of the carcinoma: squamous metaplasia contributes to the pathogenesis of breast abscess and the squamous epithelium of the ducts can subsequently undergo carcinomatous change, with invasion as part of a stepwise progression. Chronic inflammation, long-standing ulcers and persistent irritation can possibly sustain a neoplastic differentiation (11). Our case arose 15 years after post-surgical local radiation for a primary adenocarcinoma of breast. We found only one other case of primary SCC after previous adjuvant radiation therapy of the breast in the literature (5). Another case is reported after radiation therapy for Hodgkin's disease (12).

Ultrasonography is more useful than mammography in diagnosis of these lesions, as microcalcifications most frequently are absent, as they were in our patient (13). Pathological and clinical criteria are required for diagnosis. To date, surgical treatment is the same as that of more common subtypes of breast cancer, with conservative surgery

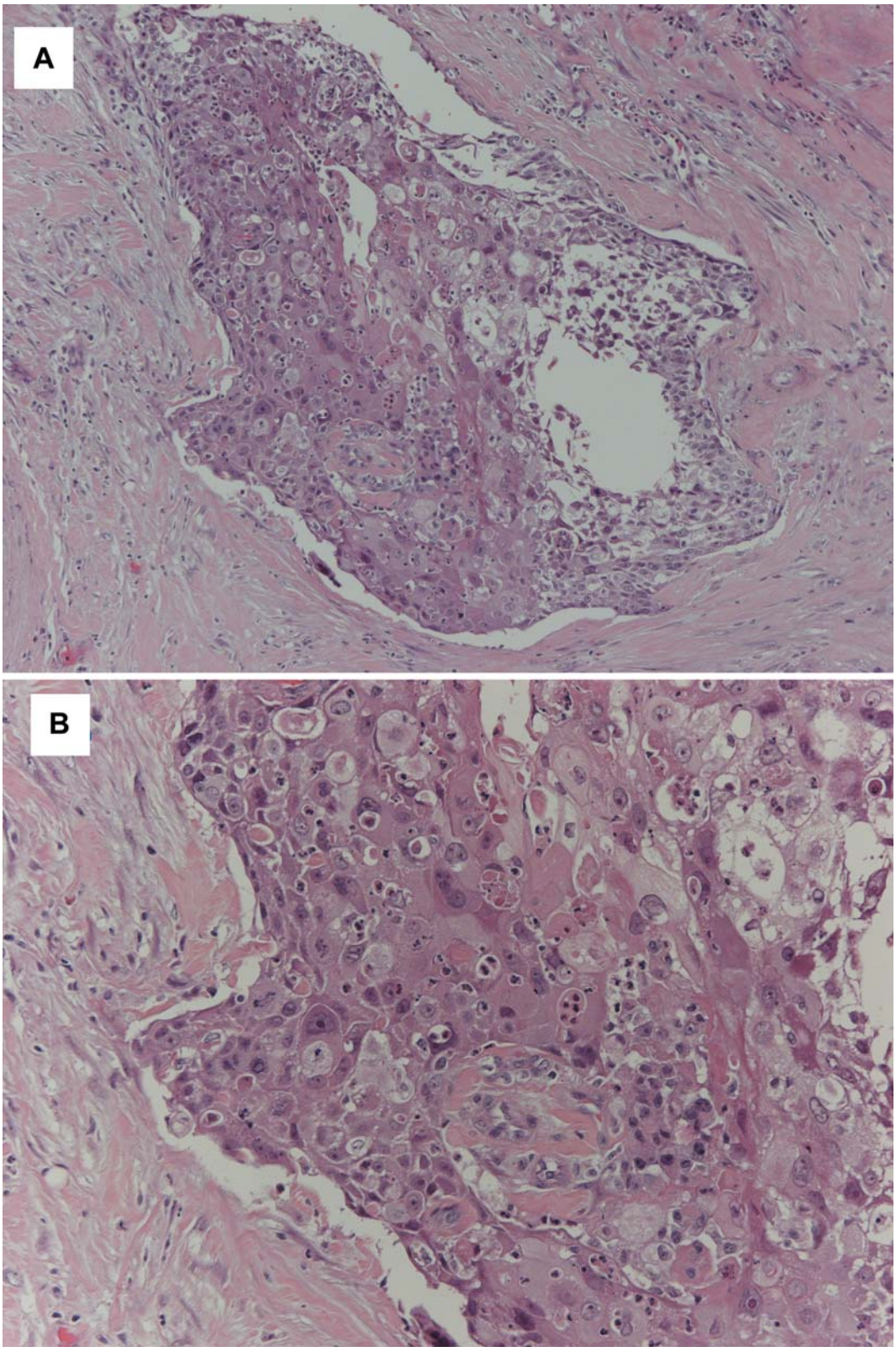

Figure 1. *Microscopic sections of the tumor showing clusters of malignant squamous cells with cytoplasmatic keratinization. H&E stain; A ×50, B ×200 magnification.*

and lymph node dissection according to international guidelines. In a review of 92 cases of patients with SSC of the breast-Behranwala reported that about 70% had no axillary nodal metastases (14).

This histotype usually has a high grade of proliferation and is negative for hormonal receptor expression (15). It can include a ductal carcinoma component and thus be treated as ductal carcinoma (16).

Because of the low incidence, there are no randomized studies, so the optimum choice of chemotherapeutic agents is still to be determined. Rostock *et al*. in their review suggest that SCC is not sensitive to chemotherapeutic agents commonly used for ductal carcinoma, such as cyclophosphamide, fluorouracil and adriamycin (13). Other authors recommend the use of fluorouracil and cisplatinum with or without doxorubicin (15).

The role of radiation is unclear. Despite the fact that SCC is generally considered to be radiosensitive (9), radiotherapy has been used only in few patients (14). The squamous histotype of breast cancer is considered very aggressive and treatment-refractory, with poor prognosis, (17) but outcome may be more a function of the stage at diagnosis rather than the histologic subtype (18).

In conclusion, there are no specific guidelines for the treatment of primary SCC of the breast. Larger series are necessary to determinate if different strategies of treatment and follow-up are necessary and if prognosis is really comparable to that of other histotypes of cancer of the breast.

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Received August 4, 2014
Revised September 18, 2014
Accepted September 25, 2014